Technical Abstract

Many diseases lead to kidney failure, including diabetes, uncontrolled hypertension, atherosclerosis, glomerulonephritis and polycystic kidney disease. Because the kidney is the primary source of erythropoietin (EPO), severe chronic anemia is a universally associated complication of end stage renal disease (ESRD). Erythropoietin is a 30 Kd glycoprotein hormone that regulates red cell production and maintenance in mammals. The human erythropoietin gene has been cloned. The availability of recombinant human EPO has provided a major advance in the treatment of renal failure in patients who are receiving dialysis. The attendant dangers of transfusion therapy were eliminated and the quality of life of these patients has significantly improved. This treatment given 2-3 times weekly raises hematocrit and hemoglobin levels and improves cardiovascular status. In the US, the estimated cost of erythropoietin for the 214,000 people with anemia of chronic renal failure is $1.3 billion annually. Thus, the ability to treat these patients and others with erythropoietin responsive anemias by gene therapy would provide a major clinical and economic benefit.

The goal of this protocol is to provide a gene therapy method for the sustained delivery of erythropoietin to treat the anemia of patients with ESRD. Patients will be implanted with polytetrafluoroethylene (PTFE) hemodialysis access grafts seeded with autologous vascular smooth muscle cells retrovirally transduced to express human EPO. When primary arteriovenous fistulas are made approximately 5 cm of vein not needed for hemodialysis access will be available for harvest of autologous smooth muscle cells. If a patient's native arteriovenous fistula does not mature we propose that a PTFE graft seeded with autologous EPO expressing smooth muscle cells will be placed at the site of the immature fistula. The method of EPO delivery we propose will involve no extra surgery for study patients other than that currently required to impant their dialysis access grafts. The disease-associated anemia occurs in all patients and therefore is predictable enough to allow meaningful assessment of the results of gene therapy by measurement of hematocrit. We have shown that transduced vascular smooth muscle cells will provide sustained EPO expression and can be returned to animals in PTFE vascular grafts. The amount of EPO required to prevent anemia in ESRD patients ranges from 12 to 500 U per kg per week, with an average dose being about 75 U per Kg per week. For an 80 kg patient this would bc 6000 U per week. Our data from access grafts seeded with human vascular smooth muscle cells retrovirally transduced to express human EPO, indicate a 10 cm graft would deliver EPO at this level. We will determine the amount of EPO secreted from transduced patient cells and use this value to seed a predetermined number into PTFE dialysis grafts. Using this approach of controlling the number of cells implanted in the PTFE access graft we can control the delivery of EPO.